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Synthesis in the Diazasteroid Group. XXI. An Alternative Synthesis of the 8,16-Diazasteroid System

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6,7-Dihydro-6-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridine (**1**) was heated with 3,4-methylenedioxyphenethyl bromide to give the corresponding quaternary bromide (**2**), which was subjected to catalytic hydrogenation to afford 2,3-methylenedioxy-16-methyl-17-oxo-8,16-diaza-9,10-seco-estra-1,3,5(10)-triene (**5**). The cyclization of **5** was achieved with mercuric acetate in 5% acetic acid solution, leading to 2,3-methylenedioxy-16-methyl-17-oxo-8,16-diaza-estra-1,3,5(10)-triene (**7**). The structure of **7** was established by X-ray crystallographic analysis.

Keywords——8,16-diazasteroid; oxidative cyclization; mercuric acetate oxidation; 5*H*-pyrrolo[3,4-*b*]pyridine; X-ray analysis

We have been engaged in the synthesis of diazasteroid group compounds for more than ten years, in view of the possible physiological activities of such compounds. We previously established the synthesis of the 8,16-diazasteroid system together with the 8,17-diazasteroid system, starting with 1-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline and 3-pyrrolidinone derivatives.[1] However, the product incorporated a vinylogous lactam moiety in the molecule as depicted in Chart 1 (a and b), and accordingly no stereochemistry came into question. This paper presents an alternative synthesis of the 8,16-diazasteroid system which bears no vinylogous lactam moiety. The stereochemistry of the product was established by X-ray crystal structure analysis.

The strategy here was to start with the C/D ring and then develop the whole structure of the molecule. Thus 6,7-dihydro-6-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridine (**1**), which had been prepared by Dobeneck *et al.*,[2] was treated with an equivalent quantity of 3,4-methylenedioxyphenethyl bromide to afford 1-(3′,4′-methylenedioxyphenethyl)-6,7-dihydro-6-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridinium bromide (**2**) in good yield. This compound was identified on the basis of the mass spectrum (MS), infrared (IR) spectrum and elemental analysis. Three tactics for the whole ring fusion were attempted (Chart 1, paths A, B and C). Path A: Ferricyanide oxidation[3] of **2** in a usual manner to provide the corresponding 5*H*-pyrrolo[3,4-*b*]pyridine-2,5-dione (**3**), followed by Bischler–Napieralski ring closure to give the target compound. Path B: Sodium borohydride reduction of **2** after the synthesis of the hexahydro-indolo[2,3-*a*]quinolizine according to Fry *et al.*[4]

However, both path A and path B were unsuccessful. Next, path C was investigated.

The quaternary ammonium bromide **2** dissolved in 50% aqueous methanol was hydrogenated over platinum oxide (3 mol of hydrogen was absorbed), and pale yellow pillars (mp 73 °C) were obtained in good yield. This compound showed only one spot on thin-layer chromatography, and was identified as 2,3-methylenedioxy-16-methyl-17-oxo-8,16-diaza-9,10-seco-estra-1,3,5(10)-triene (**5**) on the basis of elemental analysis, IR and nuclear magnetic

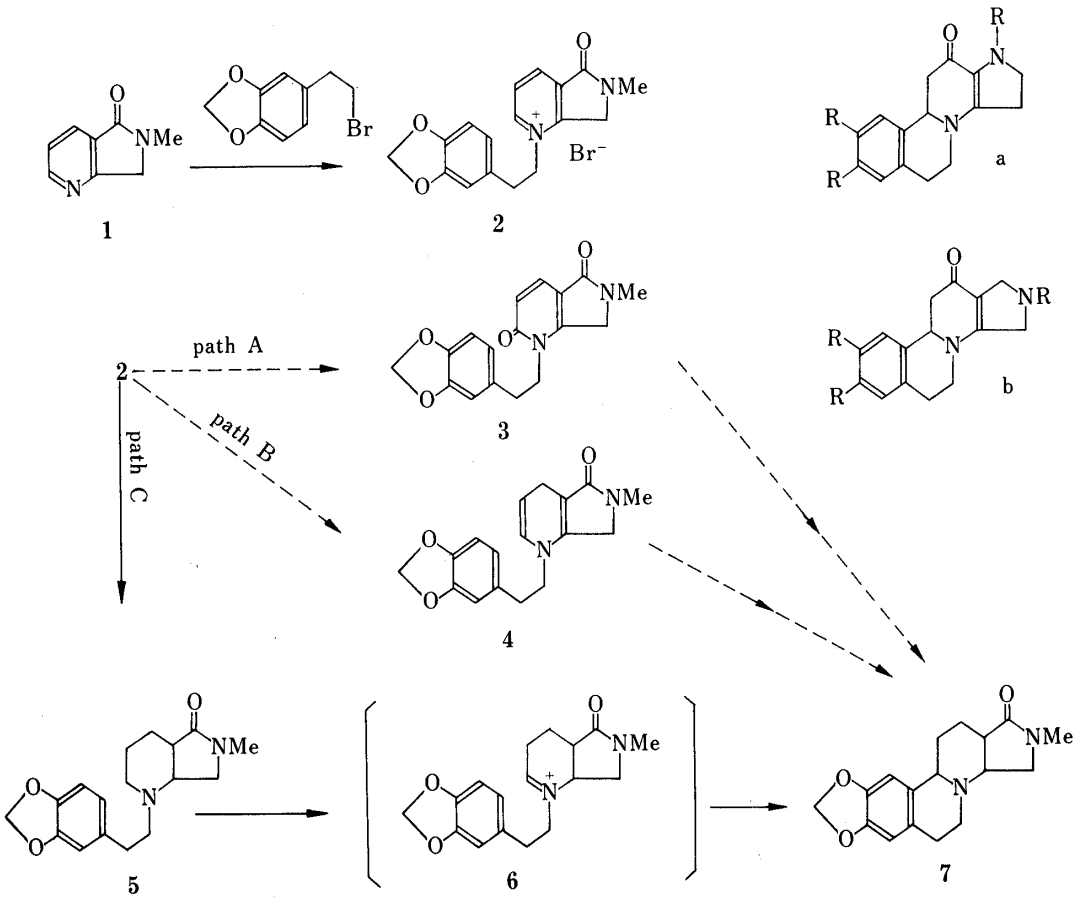
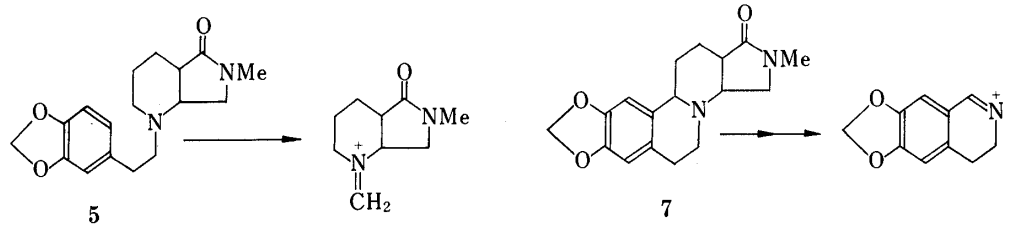


Chart 1

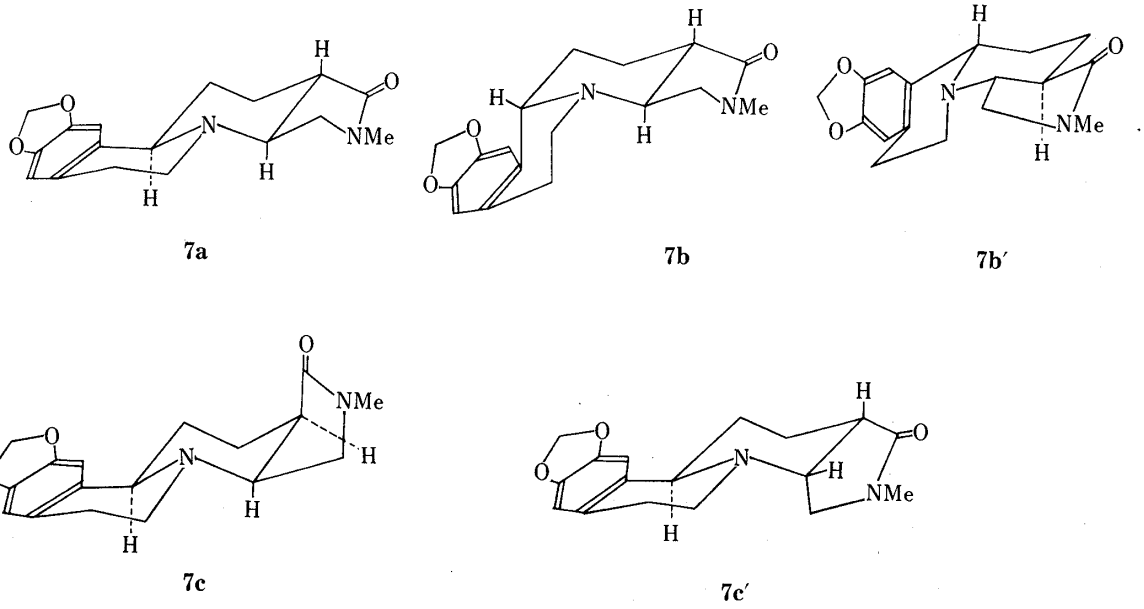
resonance (NMR) spectra, and MS (base ion peak *m/e* 167, molecular ion peak *m/e* 302).

Compound **5** was successively subjected to mercuric acetate oxidation[5] in 5% aqueous acetic acid solution and then to sodium borohydride reduction to afford colorless needles (mp 174 °C) in 40% yield. The product was identified as the target compound, 2,3-methylenedioxy-16-methyl-17-oxo-8,16-diaza-estra-1,3,5(10)-triene (**7**) on the basis of elemental analysis, MS (Chart 2; comparatively stable fragment peak *m/e* 175 due to 6,7-methylenedioxy-3,4-dihydroisoquinoline), and the NMR spectrum. The NMR spectrum lacked the three aromatic protons (δ 6.4—7.3 ppm) of compound **5**, and showed two aromatic protons at δ 6.55 and at δ 6.60 ppm (each singlet) instead, thus suggesting A/B ring fusion. In the above reaction process, compound **5** was subjected to oxidative dehydrogenation to afford **6**, which probably underwent successive annelation to **7** in the acetic acid medium.



m/e 302 *m/e* 167 *m/e* 300 *m/e* 175

Chart 2



7a 7b 7b′

7c 7c′

Chart 3

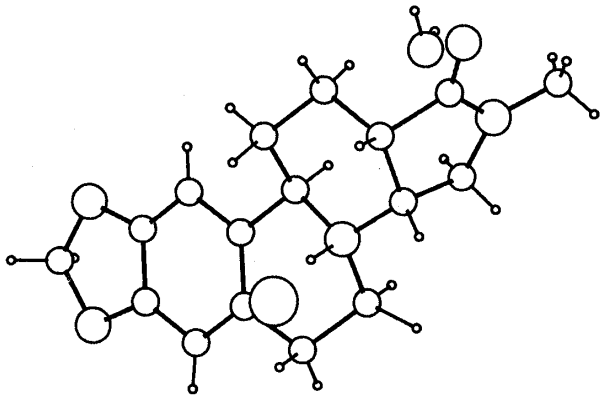


Fig. 1. Molecular Structure of 7-HBr

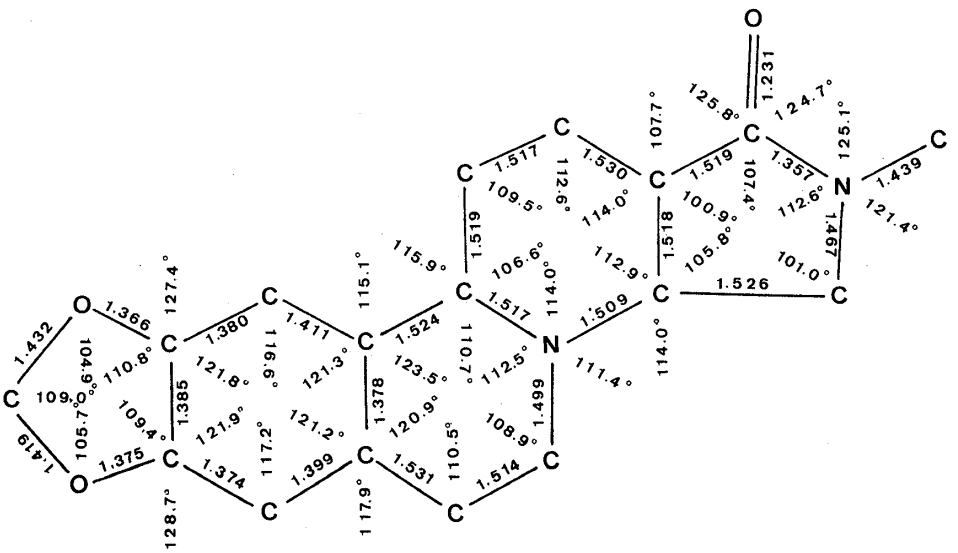


Fig. 2. Bond Angles and Distances

TABLE I. Atomic Coordinates ($\times 10^3$) for the Hydrogen Atoms, with Estimated Standard Deviations in Parentheses

	X	*Y*	*Z*
H (1)	551 (12)	192 (3)	205 (13)
H (4)	79 (9)	279 (2)	27 (10)
H (6A)	−73 (9)	217 (2)	−118 (9)
H (6B)	−80 (12)	196 (3)	73 (13)
H (7A)	67 (15)	156 (4)	−213 (16)
H (7B)	−132 (11)	132 (3)	−128 (12)
H (8)	43 (10)	134 (2)	137 (11)
H (9)	346 (10)	134 (2)	−31 (11)
H (11A)	272 (16)	122 (3)	364 (17)
H (11B)	482 (13)	128 (3)	299 (13)
H (12A)	401 (10)	56 (2)	304 (11)
H (12B)	450 (15)	70 (3)	97 (16)
H (13)	128 (14)	48 (3)	223 (15)
H (14)	−32 (10)	74 (2)	3 (11)
H (15A)	266 (9)	83 (2)	−234 (10)
H (15B)	64 (10)	69 (2)	−321 (11)
H (20A)	618 (12)	323 (3)	85 (12)
H (20B)	580 (14)	320 (3)	326 (15)
H (22A)	231 (10)	−25 (2)	−294 (10)
H (22B)	355 (13)	5 (3)	−348 (13)
H (22C)	166 (16)	1 (4)	−447 (17)
H (WA)	651 (11)	66 (3)	−210 (12)
H (WB)	673 (15)	86 (4)	−378 (17)

The stereochemistry of 8-azasteroids has been reported in detail,[6] and can be classified into three categories, as follows. A) In the case of *trans* fusion of both the B/C ring and the C/D ring, intensive Bohlmann bands in the IR are observed, and the NMR signal of the 9-proton appears as a quartet at high field, $\delta < 3.2$ ppm. B) In the case of B/C ring *cis* fusion and C/D ring *trans* fusion, no Bohlmann bands in the IR appear, and the NMR signal of the 9-proton should appear as a triplet or a quartet at low field, $\delta > 4.2$ ppm. C) In the case of B/C ring *trans* fusion and C/D ring *cis* fusion, conformational isomers (Chart 3) due to the coordination of the substituent at the 13-position are expected. In *syn–cis*[7] **7c** Bohlmann bands are clearly observed, and the NMR signal of the 9-proton appears at δ 3.2 ppm as a quartet. In *anti–cis* **7c′**, no Bohlmann bands appear, and the NMR signal of the 9-proton is observed at δ 3.6—3.8 ppm as a quartet.

Based on the above empirical results, we will discuss the stereochemistry of compound **7** prepared here. Compound **7** displays no Bohlmann bands, and the NMR signal of the 9-proton appears at δ 3.72 ppm as a double doublet ($J_{ae} = 6$, $J_{aa} = 12$ Hz), thus suggesting B/C *trans* fusion and C/D *cis* fusion. In addition, the 9-proton and the 13-proton may be *anti* to each other. From the above data and the description in category C it was postulated that **7** has the *anti–cis* **7c′** structure (category C). However, this conclusion was not definitive. Therefore, X-ray crystal structure analysis of the hydrobromide (mp 223 °C) of **7** was carried out. The results confirmed the validity of the above reasoning.

From the result of the X-ray analysis, the A, B, C ring system as a whole is approximately planar, and the D ring forms a considerable angle with the A B C plane. The structure of each ring is as follows; A is planar, B is a half-chair form, C is a chair form, and D is a C-14 envelope type. A stereoscopic view of the molecular structure is shown in Fig. 1. Bond lengths and angles are given in Fig. 2. Tables I and II, show atomic coordinates for hydrogen and non-hydrogen atoms, respectively.

TABLE II. Atomic Coordinates ($\times 10^4$, $\times 10^5$ for Br) and Equivalent Isotropic Thermal Parameters for the Nonhydrogen Atoms, with Estimated Standard Deviations in Parentheses

	X	*Y*	*Z*	B_{eq}
Br	−14361 (11)	12416 (3)	38345 (12)	4.1
C(1)	4585 (9)	2058 (2)	1569 (10)	2.8
C(2)	4722 (9)	2487 (2)	1629 (10)	2.7
C(3)	3313 (10)	2742 (2)	1143 (10)	2.7
C(4)	1712 (10)	2584 (2)	522 (11)	2.8
C(5)	1548 (9)	2150 (2)	438 (10)	2.3
C(6)	−207 (9)	1969 (2)	−317 (11)	2.9
C(7)	50 (9)	1539 (2)	−1140 (11)	2.9
N(8)	1013 (7)	1274 (2)	321 (8)	2.2
C(9)	2878 (8)	1421 (2)	758 (10)	2.3
C(10)	2940 (9)	1894 (2)	951 (9)	2.2
C(11)	3574 (10)	1176 (2)	2479 (12)	3.3
C(12)	3652 (10)	717 (2)	1980 (11)	3.3
C(13)	1864 (9)	542 (2)	1297 (11)	2.8
C(14)	863 (9)	815 (2)	−142 (11)	2.5
C(15)	1534 (10)	699 (2)	−2069 (11)	3.1
N(16)	1978 (9)	258 (2)	−1763 (9)	3.3
C(17)	2184 (10)	158 (2)	104 (13)	3.5
O(18)	2578 (9)	−191 (2)	718 (10)	4.7
O(19)	6176 (7)	2718 (2)	2135 (9)	4.1
C(20)	5636 (11)	3142 (3)	1868 (12)	3.6
O(21)	3817 (8)	3151 (2)	1344 (8)	3.7
C(22)	2439 (14)	−6 (3)	−3306 (15)	5.0
OW	5869 (11)	834 (3)	−2904 (14)	8.2

$B_{eq} = 4/3 \sum_i \sum_j \beta_{ij} a_i a_j$.

From the above results, we speculated that the pyrrolo[3,4-*b*]pyridinium salt **2** underwent *cis* hydrogenation, and in the subsequent oxidative ring closure, the benzene ring approached the C ring from the sterically less hindered direction, in other words, from the opposite side with respect to the pyrrole ring bent towards the C ring.

The physiological effects of the compounds synthesized here are now being examined.

Experimental

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken with a JASCO A-102 spectrophotometer. NMR spectra were recorded on a JEOL PMX-60 or a Varian LX-200 spectrometer using tetramethylsilane as an internal standard. MS were obtained with a JEOL-JMS-D200 spectrometer at 70 eV.

1-(3′,4′-Methylenedioxyphenethyl)-6,7-dihydro-6-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridinium Bromide (2)——A mixture of 6,7-dihydro-6-methyl-5-oxo-5*H*-pyrrolo[3,4-*b*]pyridine[2] (3 g, 20 mmol) and 3,4-methylenedioxyphenethyl bromide (4.6 g, 20 mmol) was heated at 90 °C for 24 h. The resultant solid mass was recrystallized from aq. MeOH to afford **2** as light brown needles (2.3 g), mp 264 °C, IR ν_{max}^{Nujol} cm^{-1}: 1700 (CO), *Anal.* Calcd for $C_{17}H_{17}BrN_2O_3$: C, 54.12; H, 4.63; N, 7.43. Found: C, 53.86; H, 4.51; N, 7.13.

2,3-Methylenedioxy-16-methyl-17-oxo-8,16-diaza-9,10-seco-estra-1,3,5(10)-triene (5)——A solution of **2** (3.7 g, 10 mmol) in 100 ml of 50% aqueous MeOH was hydrogenated over PtO_2 (0.3 g) catalyst at room temperature under atmospheric pressure. After shaking of the mixture for 9 h, 3 eq of H_2 had been absorbed. The catalyst and the solvent were removed to give a solid mass, which was neutralized with 10% Na_2CO_3 in the cold. The solution was extracted with ether, dried over anhydrous $MgSO_4$, and worked up in the usual manner to give a pale brownish oil. The oil was purified through alumina with benzene as an eluant to afford pale yellow pillars (2.4 g, 82%), which were

recrystallized from benzene–isopropyl ether (1 : 1), mp 74 °C, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO), NMR ($CDCl_3$) δ (ppm): 2.76 (3H, s, $=NCH_3$), 5.90 (2H, s, –O–CH_2–O–), 6.20—7.77 (3H, m, aromatic). MS: *m/e* 302 (M^+), *m/e* 167 base peak. *Anal.* Calcd for $C_{17}H_{22}N_2O_3$: C, 67.52; H, 7.33; N, 9.27. Found: C, 67.54; H, 7.36; N, 9.12.

2,3-Methylenedioxy-16-methyl-17-oxo-8,16-diaza-estra-1,3,5(10)-triene (7)——A solution of **5** (5 g, 17 mmol) and mercuric acetate (27 g, 85 mmol) in 5% aqueous AcOH (300 ml) was stirred at 90 °C for 1 h and then treated with H_2S for 1 h at the same temperature. After filtration of the mixture through Celite and careful washing of the filter cake with aqueous AcOH, the combined filtrates were concentrated *in vacuo* to a small volume and diluted with 75% aqueous EtOH (50 ml). The pH was brought to about 6 with saturated aqueous $NaHCO_3$, $NaBH_4$ was added in excess (0.7 g) under ice-cooling, and the mixture was left at room temperature overnight. The reaction mixture was acidified with AcOH and concentrated *in vacuo* to leave a brownish oil. The oil was neutralized with saturated aqueous Na_2CO_3, and extracted with $CHCl_3$. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give brown crystals (2 g, 40%) after removal of the solvent. Recrystallization from AcOH : EtOH (4 : 1) gave colorless needles, mp 173 °C, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (CO). NMR ($CDCl_3$) δ (ppm): 2.89 (3H, s, $=NCH_3$), 3.72 (1H, dd, $J_{ae}=6$, $J_{aa}=12$ Hz, C-9), 5.91 (2H, s, –O–CH_2–O–), 6.55 (1H, s, aromatic), 6.60 (1H, s, aromatic). MS: *m/e* 300 (M^+), *m/e* 299 (M^+-1) base peak, *m/e* 175. *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.85; H, 6.69; N, 9.24.

Crystal Data——$C_{17}H_{20}N_2O_3 \cdot HBr \cdot H_2O$, M = 399.29, Monoclinic $a=7.639$ (1), $b=32.097$ (5), $c=7.058$ (1) Å, $\beta=93.11$ (1)°, $V=1728.0$ (4) Å^3, $Dc=1.535$ g/cm^3, $Z=4$. Space group $P2_1/c$.

Crystallographic Measurements——Single crystals of **7** were obtained from water by slow evaporation. The intensity data were collected by the 2θ–ω scanning technique using graphite-monochromated CuK_α radiation on a four-circle diffractometer (Rigaku AFC-5). Of the total of 2939 independent reflections, 1918 had intensities above the $2.667\sigma(1)$ level and they were used for structure determination.

Determination of the Structure——The structure was solved by direct methods using MULTAN and refined by the block-diagonal least-squares method with anisotropic temperature factors for all non-hydrogen atoms and with isotropic ones for all hydrogen atoms. The final R value was 0.063.

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References

1) T. Yamazaki, K. Matoba, K. Isomura, and M. Nagata, *J. Heterocycl. Chem.*, **11**, 503 (1974).
2) H. Dobeneck and B. Hansen, *Chem. Ber.*, **105**, 3611 (1972).
3) R. A. Aramovitch and A. R. Vinutha, *J. Chem. Soc.* (*B*), **1971**, 131; T. Fujii, M. Ohba, S. Yoshifuji, and M. Kirisawa, *Chem. Pharm. Bull.*, **25**, 2887 (1977); T. Fujii, K. Yoshida, M. Ohba, M. Mitsukuchi, I. Tanaka, S. Yoshifuji, and M. Kirisawa, *ibid.*, **25**, 2072 (1977).
4) E. M. Fry and J. A. Beisler, *J. Org. Chem.*, **35**, 2809 (1970).
5) E. Wenkert and B. Wickberg, *J. Am. Chem. Soc.*, **84**, 4914 (1962).
6) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.*, **86**, 3346 (1964); H. Bruderer, M. Baumann, M. Uskoković, and A. Brossi, *Helv. Chim. Acta*, **47**, 1852 (1964); R. E. Brown, D. M. Lustgarten, R. J. Stanaback, and R. I. Meltzer, *J. Org. Chem.*, **31**, 1489 (1966); A. H. Reine and A. I. Meyers, *ibid.*, **35**, 554 (1970); R. E. Brown, A. I. Meyers, L. M. Trefonas, R. L. R. Towns, and J. N. Brown, *J. Heterocycl. Chem.*, **8**, 279 (1971).
7) Here *syn* and *anti* refer to the relative configurations of the angular hydrogen at C-9 and the hydrogen at C-13.